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Divergent Regioselectivity in the Base-Promoted Reactions of Cyclic Eight-Membered α-Ketols with Activated Halides

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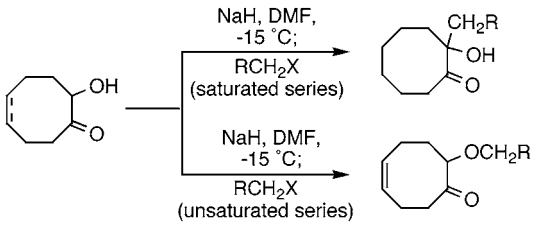
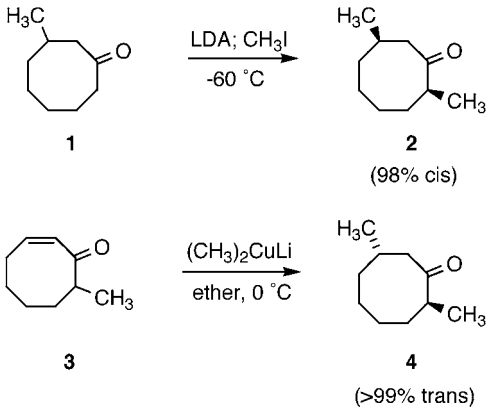
ABSTRACT



Deprotonation of 2-hydroxycyclooctanone followed by exposure to an allylic or benzylic halide proceeds very selectively to give the product of *C*-alkylation. The effect of $\Delta^{5,6}$-unsaturation is to promote instead the formation of the *O*-alkylated derivative. This crossover in kinetic preference is attributed to an inability of the olefinic system to attain a conformation conducive to proton abstraction at C-2.

As a result of the application of several physical methods including NMR analysis,[1] X-ray diffraction,[2] and molecular mechanics calculations,[3] functionalized eight-membered-ring compounds are recognized to adopt essentially homogeneous conformations in their ground state.[4] The controlling features include the minimization of angular strain, eclipsing interactions, and nonbonded transannular repulsion.[5] In combination, these effects are influential in exerting profound consequences on the stereochemical course of reactions involving cyclooctanoid systems. The conversion of **1** to **2** and the addition of lithium dimethylcuprate to **3** with generation of **4** constitute two examples of the level of effectiveness with which remote asymmetric induction can be realized with cyclic ketones of this class.[4] The two π-surfaces in the enolate ion $\mathbf{1}^-$ and in enone **3** are sterically very different. The conformational bias provided by the resident methyl substituent is presumably sufficient to guarantee the predominant generation of diastereomeric dimethyl products by reagent capture from the less hindered direction.



(1) (a) Anet, F. A. L.; Hartman, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 1204. (b) Anet, F. A. L.; St. Jacques, M. *J. Am. Chem. Soc.* **1966**, *88*, 2585, 2586. (c) Anet, F. A. L.; Cheng, A. K.; Krane, J. *J. Am. Chem. Soc.* **1973**, *95*, 7877.

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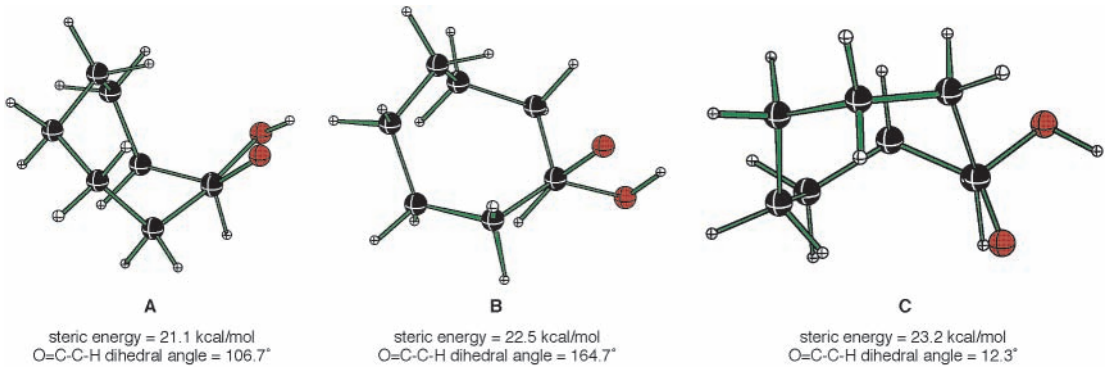


Figure 1. The three lowest energy conformations of **5**.

The experiments reported here demonstrate that pronounced regioselectivity differences can accompany the crossover from saturated to transannularly unsaturated eight-membered α-ketols exemplified by **5** and **6**. As shown in

5 **6**

Figure 1, 2-hydroxycyclooctanone (**5**) can adopt three low-energy conformations as gauged by MM3 calculations.[6] Of these, the energy minimum possesses the hydrogen-bonded arrangement **A** (21.1 kcal/mol). When viewed via a modified Newman projection down the carbonyl−carbinol bond, the O═C−C−H dihedral angle is seen to be 106.7°, a value approaching that deemed to be ideal for maximum stereoelectronic overlap.[7] Moreover, the abstraction of this proton would generate a low-energy *Z*-enolate.[8] Release of the hydrogen-bonding constraint leads to conformers **B** (22.5 kcal/mol) and **C** (23.2 kcal/mol), both of which are unattractive candidates for α-deprotonation. Thus, **B** would serve as a likely precursor to a highly strained *E*-enolate, and **C** suffers from severe misalignment of the neighboring C−H bond.

The consequences of introducing an unsaturated linkage as in **6** on the prevailing conformational topology is quite dramatic (Figure 2). The lowest energy conformation can expectedly be traced to the hydrogen-bonded structure **D**. Intimately associated with the structural features of **D** is a O═C−C−H dihedral angle of 164.0°. Like **B**, α-deprotonation from this arrangement is improbable since an *E*-enolate would likely materialize. The dispositions of the α-proton in structures **E** and **F** are similarly nonconducive to enolate formation in light of the dihedral angles involved (168.2° and −46.0°).

We rationalized **A**−**F** to reflect an unparalleled ability of **5** to experience *C*-alkylation when deprotonated with a suitable base and exposed subsequently to an electrophilic halide. We considered it reasonable to assume that the alkali metal ion from the base would foster adoption of a conformation akin to that present in **A**, where coordination of M^+ to both oxygens is conveniently accessible. At the experimental level, treatment of **5** with sodium hydride (1.3 equiv) in DMF at −15 °C followed by an allylic or benzylic halide resulted in smooth conversion to α-ketols **7** (Table 1). Processing **6** in an entirely comparable manner afforded instead the α-alkoxy ketones **8** (Table 2).[9] All reported yields relate to material purified by chromatography on silica gel and are not maximized. Control experiments have provided

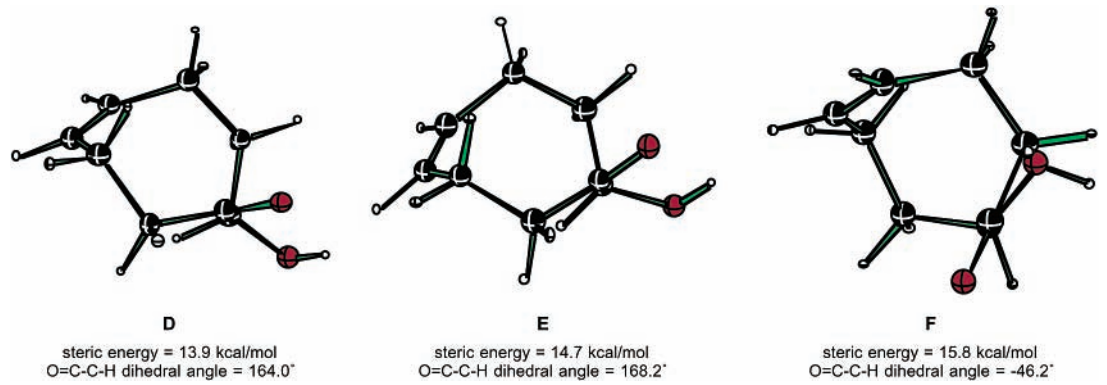


Figure 2. The three lowest energy conformations of **6**.

Table 1. Alkylation Products from **5**

5 **7**

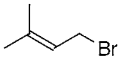
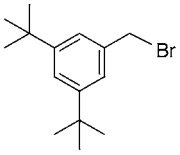
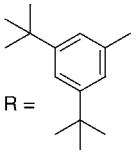
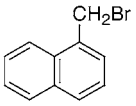
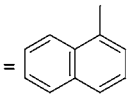
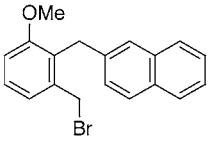
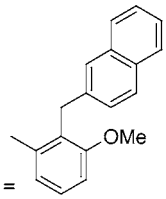
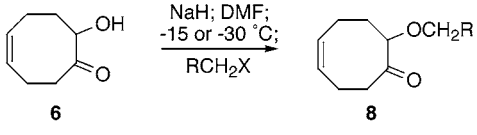
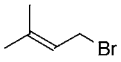
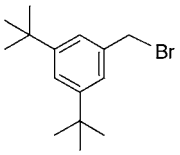
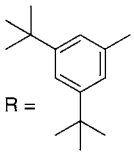
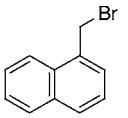
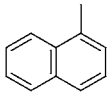
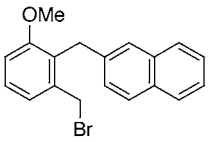
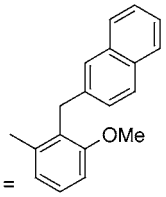
run no.	halide	product	yield,%
1	$CH_2 = CHCH_2Br$	R = $CH=CH_2$	56
2		R = $CH=CMe_2$	60
3	$C_6H_5CH_2Br$	R = C_6H_5	42
4	*p*-$MeOC_6H_4CH_2Br$	R = *p*-$MeOC_6H_4$-	62
5	*p*-$CF_3C_6H_4CH_2Br$	R = *p*-$CF_3C_6H_4$-	43
6		R = 	40
7		R = 	45
8		R = 	40

Table 2. Alkylation Products from **6**



6 **8**

run no.	halide	product	yield,%
9	$CH_2 = CHCH_2Br$	R = $CH=CH_2$	61
10		R = $CH=CMe_2$	73
11	$C_6H_5CH_2Br$	R = C_6H_5	50
12	*p*-$MeOC_6H_4CH_2Br$	R = *p*-$MeOC_6H_4$-	70
13	*p*-$CF_3C_6H_4CH_2Br$	R = *p*-$CF_3C_6H_4$-	51
14		R = 	43
15		R = 	69
16		R = 	46

an indication that neither **5** nor **6** is completely stable under the alkaline conditions applied here. In the absence of alkylating agent, only 75% of **5** and 90% of **6** could be recovered.

No byproduct was formed at a level sufficient to permit possible isolation and characterization. In no instance was evidence gained for the formation of that isomer where alkylation may have occurred away from the α-hydroxyl group. This impressive regiochemical control may be traced to the mechanistic features of the process outlined above.

The distinction between **7** and **8** is readily made on the basis of ^{1}H NMR. While the CH_2 group from the alkylating agent is bonded to saturated carbon in **7**, it is linked to oxygen in **8**. Other differences such as the presence or absence of the C-2 proton are equally evident. Remarkably, in no instance was cross-contamination of products observed.

Consequently, the conversion of tetrahedral carbon to trigonal carbon at C-2 in **5** is particularly facile. While enolate generation may be preceded by ionization of the geminal hydroxyl, subsequent proton transfer from the adjoining C−H bond operates smoothly via conformer **A** for the reasons advanced above. The chelative assimilation of a larger sodium ion into **A** is likely to be accompanied by a more perfect dihedral angle alignment. On the basis of the divergent chemical reactivity of **6**, a geometry equivalently favorable to α-deprotonation is obviously not populated as readily. The ability of a transannularly disposed double bond to provide conformational constraints such that adoption of a different reaction pathway is directly impacted has not been previously recognized. The consequences of this phenomenon should be more far-reaching than the series of observations recorded here.

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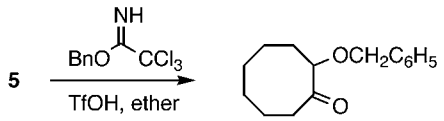
(8) Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 5994.

(9) The bromide utilized in runs 8 and 16 was generated from the carboxylic acid via a three-step sequence: (a) K_2CO_3, Me_2SO_4, acetone; (b) $LiAlH_4$; (c) PBr_3. The carboxylic acid was prepared more than two decades ago by Prof. Melvin S. Newman: Newman, M. S.; Kanakarajan, K. *J. Org. Chem.* **1980**, *45*, 2301.

Direct access to *O*-benzylated cyclooctanones such as **9** can be alternatively realized simply by making recourse to acidic conditions such as those involving a trichloroacetimidate reagent. Informatively, the α-benzyloxycyclooctanone **9** does not undergo equilibration with **7** (R = C_6H_5) when treated with sodium hydride in DMF.[10]



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Supporting Information Available: General experimental details and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027315Z

(10) (a) Paquette, L. A.; Zeng, Q. *Tetrahedron Lett*. **1999**, *40*, 3823. (b) Curtin, D. Y.; Leskowitz, S. *J. Am. Chem. Soc*. **1951**, *73*, 2633. (c) Curtin, D. Y.; Proops, W. R. *J. Am. Chem. Soc*. **1954**, *76*, 494.